EXHIBIT A

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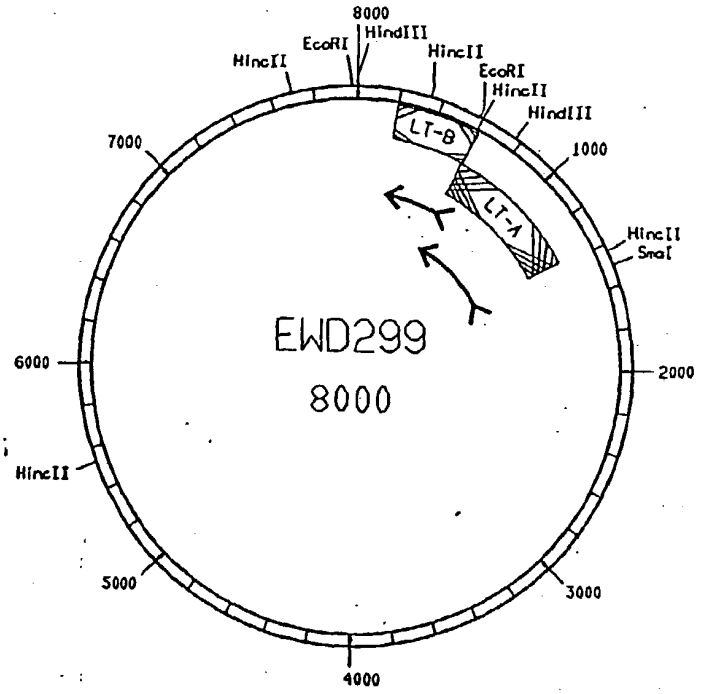
(54) Title: IMMUNOGENIC DETOXIFIED MUTANTS OF CHOLERA TOXIN AND OF THE TOXIN LT, THEIR PREPARATION AND THEIR USE FOR THE PREPARATION OF VACCINES

(57) Abstract

An immunogenic detoxified protein comprising the amino acid sequence of subunit A of cholera toxin (CT-A) or subunit A of an *Escherichia coli* heat labile toxin (LT-A) or a fragment thereof wherein one or more amino acids at, or in positions corresponding to Val-53, Ser-63, Val-97, Tyr-104 or Pro-106 are replaced with another amino acid or deleted. Examples of specific replacements include Val-53-Asp, Val-53-Glu, Val-53-Tyr, Ser-63-Lys, Val-97-Lys, Val-97-Tyr, Tyr-104-Lys, Tyr-104-Asp, Tyr-104-Ser, Pro-106-Ser. The immunogenic detoxified protein is useful as vaccine for *Vibrio cholerae* or an enterotoxigenic strain of *Escherichia coli* and is produced by recombinant DNA means by site-directed mutagenesis.



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LT2      1  -.-.FF-----T----R-A---L---QQ-AYE---PI---   38
LT1      1  ------------------FRS-----.-------------   39
LT1_1A   1  -G-R-------------R--------HN------------   40
CT       1  NDDKLYRADSRPPDEIKQSGGLMPRGQSEYFDRGTQMNIN   40

                --E-----V--NT--N------TVT--Q---I--N--GS-   78
                ----------------------------------Y-----   79
                -------------Y--------L--------A--S----Y   80
                LYDHARGTQTGFVRHDDGYVSTSISLRSAHLVGQTILSGH   80

                NE-----V-P---L-D--G---R---Y-S-N-FA------   118
                -LTIYI---...--------IS------------------   116
                ----------------------V-----Y-----------   120
                STYYIYVIATAPNMFNVNDVLGAYSPHPDEQEVSALGGIP   120

                L---I-----SF-A-EGGMQ---D--GDLF-G-TV--N--   158
                ----------------------------------------   156
                ----------N---I--R-----E------R--N----E-   160
                YSQIYGWYRVHFGVLDEQLHRNRGYRDRYYSNLDIAPAAD   160

                --Q-----SNFP-----M--STF--EQ-VPNNKEFK-GV-I   198
                ----------------------------------------   196
                --R------D-Q-------------Q---DSS-TITGD--N   200
                GYGLAGFPPEHRAWREEPWIHHAPPGCGNAPRSSMSNTCD   200

           SA-NV--KYD-MNFKKLL--RLALTFFM--D-F-GVHGE----   241
           ------------------------.-----.-----.----   236
           -E--N-STIY-R------------D-.--EV-.IY---.R---   240
           EKTQSLGVKFLDEYQSKVKRQIFSGY.QSDID.THNRI.KDEL   240
```

Figure 1